Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med 2014;370:699-708. DOI: 10.1056/NEJMoa1308573

Appendix

RTOG 0825: A randomized clinical trial of bevacizumab for newly diagnosed glioblastoma

Appendix:

Participating Sites by Affiliation In Order Of Accrual.

RTOG Institutions: Thomas Jefferson University Hospital, Arizona Oncology Services Foundation, University Of Texas-MD Anderson Cancer Center, UPMC-Shadyside Hospital, Emory University, University Of Wisconsin Hospital, Cleveland Clinic Foundation, Ohio State University Medical Center, Washington University, University Of California San Francisco, University Of Utah Health Science Center, Tel-Aviv Medical Center, St. Lukes Hospital, Allegheny-Singer Research Institute, University Of Texas Southwestern Medical School, Centre Hospitalier De L`Université De Montréal-Notre Dame, Indiana University Health Methodist Hospital, Mayo Clinic, Robert Wood Johnson University Hospital, St. Joseph Hospital, St. Vincent Hospital And Health Care Centers, Inc., Thedacare Cancer Institute, University Hospitals Of Cleveland, Maine Medical Center, Mcgill University, Penrose Cancer Center, Penrose-St. Francis Health Services, Rhode Island Hospital, MD Anderson Cancer Center – Orlando, Methodist Cancer Center, Northeast Georgia Medical Center, UCSD – University Of California, San Diego, University Of Chicago, University Of Oklahoma Health Sciences Center, Allan Blair Cancer Centre, Joe Arrington Cancer Research & Treatment Center, Kaiser Permanente Santa Clara Medical Center, Medical College Of Wisconsin, Northwestern Memorial Hospital, Parkview Cancer Center/Parkview Hospital, Radiological Associates Of Sacramento, Roswell Park Cancer Institute, Saint Barnabas Medical Center, Yale University, Abington Memorial Hospital, Anne Arundel Medical Center, Baystate Health, Dartmouth Hitchcock Medical Center, Memorial Sloan Kettering Cancer Center, New Mexico Cancer Care Alliance, Radiation Oncology Center Of Walnut Creek - John Muir Medical Center, Reading Hospital And Medical Center, Swedish Cancer Institute, Univ Of Kansas Comprehensive Cancer Center, University Of Maryland Medical Systems, University Of Rochester, Akron General Medical Center, Aultman Hospital, Community Hospitals Of Indiana Regional Cancer Care North, Florida Radiation Oncology Group / Baptist Regional, Gunderson Clinic, Maimonides Medical Center, New Mexico Oncology Hematology Consultants, Northwest Community Hospital, Piedmont Hospital, Poudre Valley Radiation Oncology, St. Alphonsus Regional Medical Center, University Of Cincinnati, University Of Iowa Hospitals And Clinics, University Of Vermont, Waukesha Memorial Hospital, Akron City Hospital, Bellin Memorial Hospital, Inc, Cancer Institute Of Cape Girardeau, City Of Hope Medical Center, Fox Chase Cancer Center, Ingalls Memorial Hospital, Loyola University Medical Center, Massachusetts General Hospital, Northeast Radiation Oncology Center, Northeastern Ontario Regional Cancer Centre, Penn State University And The Milton S. Hershey Medical Ctr, Pomona Valley Hospital Medical Center, Saint Elizabeth Regional Medical Center, St. Agnes Healthcare, St. Joseph Hospital Community Cancer Center, State University Of NY At Stony Brook, The Hospital Of Central Connecticut, The Medical Center, Inc., John B. Amos Cancer Center, Thompson Cancer Survival Center, University Of Nebraska Medical Center, University Of Texas Medical Branch, Yakima Valley Memorial Hospital, Cancer Care Associates Of Fresno Medical Group, Centracare Health System/Coborn Cancer Center, Good Samaritan Health Systems, H. Lee Moffitt Cancer Center

& Research Institute, Harrison Memorial Hospital, Hudson Valley Oncology Associates, Indiana University Health Bloomington, Inova Alexandria Hospital, James Graham Brown Cancer Ctr At University Of Louisville, John Muir Medical Center - Concord Campus, Lowell General Hospital Cancer Center, Methodist Medical Center Of Illinois, Montefiore Medical Center, Naval Medical Center/Portsmouth, Rapid City Regional Hospital, Riverview Medical Center/Riverview Regional Cancer Center, Sentara Norfolk General Hospital, South Nassau Communities Hospital, St. Lukes Hospital Association Of Duluth, Summa Health System Barberton Hospital, Suny Upstate Medical University, The Schiffler Cancer Center, University Of Alabama At Birmingham Medical Center, USON- Texas Oncology- Sugar Land. **CTSU**: Erlanger Health System, Iowa Methodist Medical Center, Lancaster General Hospital, Lehigh Valley Hospital, Florida Hospital Cancer Institution, Memorial Regional Hospital, Providence Alaska Medical Center, Wesley Medical Center, Alegent Health Immanuel Medical Center, Legacy Good Samaritan Medical Center, Memorial Medical Center, Mercy Hospital Medical Cntr, Mercy Medical Center, Meritcare Hospital, Trinity Medical Center, Via Christi Regional Medical Center.
SWOG: Sacred Heart Hospital, Southern Regional Medical Center, Good Samaritan Hospital & Medical Center, Louisiana State Univ Hospital, Memorial Medical Center, St Jude Hospital, Decatur Memorial Hospital, Edward Hospital, Martin Memorial Medical Center, Via Christi Regional Medical Center.
NCCTG: Wesley Medical Center, Boulder Community Hospital, Memorial Regional Cancer Center, Via Christi Regional Medical Center, Iowa Methodist Medical Center, Lutheran Hosp & Medical Cntr, Meritcare Clinic Bemidji, Meritcare Hospital, North Iowa Mercy Cancer Center, Porter Adventist Hospital, Providence Cancer Therapy Cntr, Rocky Mountain Center – Thornton.
CALGB: Florida Hospital, Hartford Hospital.
ECOG: Erlanger Health System, Lancaster General Hospital, Diagnostic & Treatment Center, Marshfield Clinic Cancer Center At Regional Cancer Ctr, Marshfield Clinic, Minocqua Center, Meritcare Hospital. **ACOSOG**: St Vincents Hospital, St. Joseph Regional Cancer Center.
NSABP: Hartford Hospital

Supplemental Table S1
Study Eligibility Laboratory Values

Function	Test	Acceptable Value
Hematologic	Absolute neutrophil count	≥ 1,500 10^9/l
	Platelet count	≥ 100,000 10^9/l
Renal	Serum creatinine	≤ 150µmol/l
	Blood urea nitrogen	≤ 8.9 mmol/l
Hepatic	Total serum bilirubin	≤ 34µmol/l
	Serum alanine aminotransferase	≤ 3 times the upper limit for the laboratory
	Serum aspartate aminotransferase	≤ 3 times the upper limit for the laboratory

Supplemental Table S2
Patients by Randomization Status

	Randomized (n=637)	Not Randomized (n=341)	Chi-square p-value
Age (years)			
Median	58	60	
Min - Max	19 - 82	18 - 87	
Q1 - Q3	51 - 65	52 - 67	
			0.70
<50	126 (19.8%)	71 (20.8%)	
>= 50	511 (80.2%)	270 (79.2%)	
Gender			0.15
Male	379 (59.5%)	219 (64.2%)	
Female	258 (40.5%)	122 (35.8%)	
Ethnicity			0.76
Hispanic or Latino	27 (4.2%)	12 (3.5%)	
Not Hispanic or Latino	576 (90.4%)	308 (90.3%)	
Unknown or not reported	34 (5.3%)	21 (6.2%)	
Race			0.39
American Indian/Alaska Native	2 (0.3%)	1 (0.3%)	
Asian	7 (1.1%)	2 (0.6%)	
Black or African American	11 (1.7%)	12 (3.5%)	
White	607 (95.3%)	323 (94.7%)	
More than one race	1 (0.2%)	1 (0.3%)	
Unknown or not reported	9 (1.4%)	2 (0.6%)	

Q1 = first quartile; Q3 = third quartile.

Supplemental Table S3
Patient Characteristics

Category	Bevacizumab (n = 312)	Placebo (n= 309)
Age		
< 50	57 (18%)	65 (21%)
≥ 50	255 (82%)	244 (79%)
Gender		
Male	178 (57%)	194 (63%)
Female	134 (43%)	115 (37%)
Race		
White	298 (96%)	293 (95%)
Non-white	9 (3%)	12 (4%)
Unknown	5 (1%)	4 (1%)
KPS		
60-80	124 (40%)	119 (39%)
90-100	188 (60%)	190 (61%)
Surgery		
Partial resection	107 (34%)	119 (38%)
Total resection	197 (63%)	181 (59%)
Other	8 (3%)	9 (3%)
IMRT Radiation		
Yes	242 (78%)	248 (80%)
No	70 (22%)	61 (20%)

Neurologic Function		
No symptoms	108 (35%)	105 (34%)
Minor symptoms	146 (47%)	137 (44%)
Moderate symptoms	58 (18%)	67 (22%)
MGMT Status		
Methylated	90 (29%)	85 (28%)
Unmethylated	215 (69%)	214 (69%)
Unknown (invalid, indeterminate)	7 (2%)	10 (3%)
Molecular Profile		
Favorable	82 (26%)	80 (26%)
Unfavorable	201 (64%)	201 (65%)
Indeterminate	26 (8%)	26 (8%)
Failed	3 (2%)	2 (1%)
RPA Class		
III	36 (11%)	47 (15%)
IV	222 (71%)	197 (64%)
V	49 (16%)	57 (18%)
Unknown	5 (2%)	8 (3%)

Supplemental Table S4
Patients by NCB Substudy Participation Status

	Participating (n=525)	Not participating (n=125)	Chi-square p-value
Age (years)			
Median	58	60	
Min - Max	19 - 82	25 - 82	
Q1 - Q3	51 - 65	52 - 65	
			0.65
<50	106 (20.2%)	23 (18.4%)	
>= 50	419 (79.8%)	102 (81.6%)	
Gender			0.84
Male	314 (59.8%)	76 (60.8%)	
Female	211 (40.2%)	49 (39.2%)	
Ethnicity			0.81
Hispanic or Latino	19 (3.6%)	6 (4.8%)	
Not Hispanic or Latino	478 (91.0%)	113 (90.4%)	
Unknown or not reported	28 (5.3%)	6 (4.8%)	
Race			
American Indian/Alaska Native	0 (0.0%)	2 (1.6%)	
Asian	6 (1.1%)	1 (0.8%)	
Black or African American	9 (1.7%)	2 (1.6%)	
White	503 (95.8%)	117 (93.6%)	
More than one race	1 (0.2%)	0 (0.0%)	
Unknown or not reported	6 (1.1%)	3 (2.4%)	
Education			
Grade 1 through 8 only	7 (1.3%)	5 (4.0%)	
9 - 11th grade	21 (4.0%)	5 (4.0%)	
High school graduate/GED	135 (25.7%)	39 (31.2%)	
Vocational school	32 (6.1%)	11 (8.8%)	
Associate degree/Some college	103 (19.6%)	13 (10.4%)	
Bachelor's degree	104 (19.8%)	20 (16.0%)	
Advanced degree	68 (13.0%)	13 (10.4%)	
Other	23 (4.4%)	5 (4.0%)	
Prefers not to answer	4 (0.8%)	0 (0.0%)	
Unknown	28 (5.3%)	14 (11.2%)	
KPS			0.14
70-80	202 (38.5%)	57 (45.6%)	
90-100	323 (61.5%)	68 (54.4%)	
Surgery			0.95
Other	13 (2.5%)	3 (2.4%)	
Subtotal	189 (36.0%)	47 (37.6%)	
Total (gross)	323 (61.5%)	75 (60.0%)	

Supplemental Table S4
Patients by NCB Substudy Participation Status

	Participating (n=525)	Not participating (n=125)	Chi-square p-value
Neurologic Function			0.48
No symptoms	180 (34.3%)	38 (30.4%)	
Minor symptoms	233 (44.4%)	63 (50.4%)	
Moderate symptoms	112 (21.3%)	24 (19.2%)	
MGMT Status*		Methylated vs. Unmethylated	0.63
Methylated	149 (28.4%)	33 (26.4%)	
Unmethylated	360 (68.6%)	89 (71.2%)	
Invalid	15 (2.9%)	2 (1.6%)	
Missing	1 (0.2%)	1 (0.8%)	
Molecular Profile*		Favorable vs. Unfavorable	0.19
Favorable	131 (25.0%)	36 (28.8%)	
Unfavorable	348 (66.3%)	71 (56.8%)	
Indeterminate	41 (7.8%)	16 (12.8%)	
Failed	5 (1.0%)	1 (0.8%)	
missing	0 (0.0%)	1 (0.8%)	
RPA Class			0.53
III	73 (13.9%)	14 (11.2%)	
IV	345 (65.7%)	90 (72.0%)	
V	97 (18.5%)	18 (14.4%)	
Unknown	10 (1.9%)	3 (2.4%)	

* Stratification factor.
Q1 = first quartile; Q3 = third quartile.
RPA = Recursive Partitioning Analysis.

Supplemental Table S5
Reason for Not Participating in NCB Substudy

Reason	Not Participating (n=125)	Entire Group (n=650)
Patient refused due to illness	29 (23.2%)	29 (4.5%)
Patient refused for other reason	54 (43.2%)	54 (8.3%)
Not approved by institutional IRB	1 (0.8%)	1 (0.002%)
Tool not available in patient's language	20 (16.0%)	20 (3.1%)
Other	14 (11.2%)	14 (2.2%)
Consented but not submitted	6 (4.8%)	6 (0.1%)
Missing	1 (0.8%)	1 (0.002%)

Supplemental Table S6
Pretreatment Characteristics for Randomized Patients Participating in NCB Substudy

	Bevacizumab (n=260)	Placebo (n=248)	Chi-square p-value
Age (years)			
Median	59	57	
Min - Max	21 - 82	19 - 82	
Q1 - Q3	52 - 65	50.5 - 64.5	
			0.30
<50	47 (18.1%)	54 (21.8%)	
>= 50	213 (81.9%)	194 (78.2%)	
Gender			0.17
Male	148 (56.9%)	156 (62.9%)	
Female	112 (43.1%)	92 (37.1%)	
Ethnicity			0.34
Hispanic or Latino	8 (3.1%)	11 (4.4%)	
Not Hispanic or Latino	235 (90.4%)	227 (91.5%)	
Unknown or not reported	17 (6.5%)	10 (4.0%)	
Race			
Asian	2 (0.8%)	4 (1.6%)	
Black or African American	4 (1.5%)	5 (2.0%)	
White	251 (96.5%)	235 (94.8%)	
More than one race	0 (0.0%)	1 (0.4%)	
Unknown or not reported	3 (1.2%)	3 (1.2%)	
Education			
Grade 1 through 8 only	3 (1.2%)	4 (1.6%)	
9 - 11th grade	6 (2.3%)	13 (5.2%)	
High school graduate/GED	73 (28.1%)	58 (23.4%)	
Vocational school	17 (6.5%)	15 (6.0%)	
Associate degree/Some college	41 (15.8%)	59 (23.8%)	
Bachelor's degree	54 (20.8%)	46 (18.5%)	
Advanced degree	38 (14.6%)	29 (11.7%)	
Other	12 (4.6%)	11 (4.4%)	
Prefers not to answer	1 (0.4%)	3 (1.2%)	
Unknown	15 (5.8%)	10 (4.0%)	
KPS			0.82
70-80	99 (38.1%)	92 (37.1%)	
90-100	161 (61.9%)	156 (62.9%)	
Surgery			0.40
Other	5 (1.9%)	8 (3.2%)	
Subtotal	89 (34.2%)	94 (37.9%)	
Total (gross)	166 (63.8%)	146 (58.9%)	
Neurologic Function			0.75
No symptoms	89 (34.2%)	87 (35.1%)	

Supplemental Table S6
Pretreatment Characteristics for Randomized Patients Participating in NCB Substudy

	Bevacizumab (n=260)	Placebo (n=248)	Chi-square p-value
Minor symptoms	121 (46.5%)	108 (43.5%)	
Moderate symptoms	50 (19.2%)	53 (21.4%)	
MGMT Status*			0.64
Methylated	76 (29.2%)	68 (27.4%)	
Unmethylated	178 (68.5%)	171 (69.0%)	
Invalid	6 (2.3%)	9 (3.6%)	
Molecular Profile*			0.87
Favorable	62 (23.8%)	66 (26.6%)	
Unfavorable	175 (67.3%)	160 (64.5%)	
Indeterminate	20 (7.7%)	20 (8.1%)	
Failed	3 (1.2%)	2 (0.8%)	
RPA Class			0.18
III	30 (11.5%)	40 (16.1%)	
IV	183 (70.4%)	156 (62.9%)	
V	44 (16.9%)	45 (18.1%)	
Unknown	3 (1.2%)	7 (2.8%)	

* Stratification factor.
Q1 = first quartile; Q3 = third quartile.
RPA = Recursive Partitioning Analysis.

Supplemental Table S7a
Neurocognitive Assessment Compliance

Measure	Treatment Arm	Evaluation Status	Baseline	Week 6	Week 10	Week 22	Week 34	Week 46
HVLT-R	Placebo	**Form expected**	**248**	**236**	**192**	**130**	**88**	**68**
		Completed (%)	237(96%)	194(82%)	159(83%)	99(76%)	69(78%)	60(88%)
		Form expected, but not completed	8	18	22	22	10	5
		Not tested, due to disability	0	2	3	3	1	1
		Not tested, other reason	1	12	14	15	8	2
		Discontinued, due to disability	2	0	0	0	0	0
		Discontinued, other reason	2	2	1	1	1	0
		Out of timeframe	2	0	0	0	0	0
		Unknown	1	1	4	3	0	2
		Form expected, but not received	3	24	11	9	9	3
		Form not expected	**0**	**12**	**44**	**62**	**42**	**20**
		Patient progressed	0	3	25	41	29	13
		Patient withdrew	0	3	0	1	1	1
		Patient ended protocol treatment	0	6	19	19	12	6
		Patient died	0	0	0	1	0	0
	Bevacizumab	**Form expected**	**260**	**251**	**230**	**191**	**143**	**98**
		Completed (%)	250(96%)	212(84%)	184(80%)	150(79%)	101(71%)	68(69%)
		Form expected, but not completed	9	24	36	21	25	21
		Not tested, due to disability	0	3	10	1	1	3
		Not tested, other reason	2	15	23	16	18	16
		Discontinued, due to disability	1	2	0	0	0	0
		Discontinued, other reason	1	0	2	2	3	0
		Out of timeframe	4	0	0	0	0	0
		Unknown	1	4	1	2	3	2
		Form expected, but not received	1	15	10	20	17	9

Supplemental Table S7a
Neurocognitive Assessment Compliance

Measure	Treatment Arm	Evaluation Status	Baseline	Week 6	Week 10	Week 22	Week 34	Week 46
		Form not expected	**0**	**9**	**21**	**39**	**48**	**45**
		Patient progressed	0	1	1	6	30	25
		Patient withdrew	0	5	1	2	0	0
		Patient ended protocol treatment	0	3	19	30	18	17
		Patient died	0	0	0	1	0	3
	Difference (p-value[†])		<1% (0.74)	2% (0.50)	3% (0.46)	3% (0.62)	7% (0.18)	19% (0.002)

Measure	Treatment Arm	Evaluation Status	Baseline	Week 6	Week 10	Week 22	Week 34	Week 46
TMT	Placebo	**Form expected**	**248**	**236**	**192**	**130**	**88**	**68**
Part A		Completed (%)	240(97%)	193(82%)	159(83%)	99(76%)	69(78%)	60(88%)
		Form expected, but not completed	5	19	22	22	10	5
		Not tested, due to disability	0	2	3	3	1	1
		Not tested, other reason	1	13	14	15	8	2
		Discontinued, due to disability	0	1	0	0	0	0
		Discontinued, other reason	1	1	0	0	1	0
		Out of timeframe	2	0	0	0	0	0
		Unknown	1	2	5	4	0	2
		Form expected, but not received	3	24	11	9	9	3
		Form not expected	**0**	**12**	**44**	**62**	**42**	**20**
		Patient progressed	0	3	25	41	29	13
		Patient withdrew	0	3	0	1	1	1
		Patient ended protocol treatment	0	6	19	19	12	6
		Patient died	0	0	0	1	0	0

	Bevacizumab	**Form expected**	**260**	**251**	**230**	**191**	**143**	**98**
		Completed (%)	250(96%)	210(84%)	181(79%)	148(77%)	101(71%)	64(65%)
		Form expected, but not completed	9	26	39	23	25	25
		Not tested, due to disability	1	5	9	2	3	4
		Not tested, other reason	2	15	25	16	18	18
		Discontinued, due to disability	0	2	0	0	0	0
		Discontinued, other reason	1	0	2	2	0	0
		Out of timeframe	4	0	0	0	0	0
		Unknown	1	4	3	3	4	3
		Form expected, but not received	1	15	10	20	17	9
		Form not expected	**0**	**9**	**21**	**39**	**48**	**45**
		Patient progressed	0	1	1	6	30	25
		Patient withdrew	0	5	1	2	0	0
		Patient ended protocol treatment	0	3	19	30	18	17
		Patient died	0	0	0	1	0	3
	Difference (p-value[↑])		1% (0.70)	2% (0.58)	4% (0.28)	1% (0.78)	7% (0.18)	23% (<0.001)

Measure	**Treatment Arm**	**Evaluation Status**	**Baseline**	**Week 6**	**Week 10**	**Week 22**	**Week 34**	**Week 46**
TMT	Placebo	**Form expected**	**248**	**236**	**192**	**130**	**88**	**68**
Part B		Completed (%)	237(96%)	190(81%)	157(82%)	97(75%)	69(78%)	60(88%)
		Form expected, but not completed	6	20	23	24	10	5
		Not tested, due to disability	1	2	3	3	1	1
		Not tested, other reason	2	13	15	16	8	2
		Discontinued, due to disability	0	1	0	0	0	0
		Discontinued, other reason	0	1	0	1	0	0
		Out of timeframe	2	0	0	0	0	0
		Unknown	1	3	5	4	1	2
		Form expected, but not received	5	26	12	9	9	3

	Form not expected	**0**	**12**	**44**	**62**	**42**	**20**
	Patient progressed	0	3	25	41	29	13
	Patient withdrew	0	3	0	1	1	1
	Patient ended protocol treatment	0	6	19	19	12	6
	Patient died	0	0	0	1	0	0
Bevacizumab	**Form expected**	**260**	**251**	**230**	**191**	**143**	**98**
	Completed (%)	245(94%)	209(84%)	176(79%)	146(76%)	99(69%)	64(65%)
	Form expected, but not completed	11	26	41	24	27	25
	Not tested, due to disability	2	5	9	2	3	4
	Not tested, other reason	3	16	27	15	19	18
	Discontinued, due to disability	1	1	1	1	0	0
	Discontinued, other reason	0	0	0	2	0	0
	Out of timeframe	4	0	0	0	0	0
	Unknown	1	4	4	4	5	3
	Form expected, but not received	4	16	13	21	17	9
	Form not expected	**0**	**9**	**21**	**39**	**48**	**45**
	Patient progressed	0	1	1	6	30	25
	Patient withdrew	0	5	1	2	0	0
	Patient ended protocol treatment	0	3	19	30	18	17
	Patient died	0	0	0	1	0	3
	Difference (p-value[↑])	2% (0.49)	3% (0.43)	3% (0.18)	1% (0.71)	9% (0.12)	23% (<0.001)

Measure	**Treatment Arm**	**Evaluation Status**	**Baseline**	**Week 6**	**Week 10**	**Week 22**	**Week 34**	**Week 46**
COWA	Placebo	**Form expected**	**248**	**236**	**192**	**130**	**88**	**68**
		Completed (%)	239(96%)	195(83%)	159(83%)	99(76%)	70(80%)	60(88%)
		Form expected, but not completed	5	17	22	22	9	5
		Not tested, due to disability	1	2	3	3	1	1

	Not tested, other reason	1	12	14	15	8	2
	Discontinued, due to disability	0	0	0	0	0	0
	Discontinued, other reason	0	0	0	1	0	0
	Out of timeframe	2	0	0	0	0	0
	Unknown	1	3	5	3	0	2
	Form expected, but not received	4	24	11	9	9	3
	Form not expected	**0**	**12**	**44**	**62**	**42**	**20**
	Patient progressed	0	3	25	41	29	13
	Patient withdrew	0	3	0	1	1	1
	Patient ended protocol treatment	0	6	19	19	12	6
	Patient died	0	0	0	1	0	0
Bevacizumab	**Form expected**	**260**	**251**	**230**	**191**	**143**	**98**
	Completed (%)	247(95%)	212(84%)	184(80%)	150(79%)	100(70%)	68(69%)
	Form expected, but not completed	10	24	33	20	26	21
	Not tested, due to disability	1	3	9	1	2	3
	Not tested, other reason	3	15	23	15	21	16
	Discontinued, due to disability	0	2	0	0	0	0
	Discontinued, other reason	0	0	0	1	0	0
	Out of timeframe	4	0	0	0	0	0
	Unknown	2	4	1	3	3	2
	Form expected, but not received	3	15	13	21	17	9
	Form not expected	**0**	**9**	**21**	**39**	**48**	**45**
	Patient progressed	0	1	1	6	30	25
	Patient withdrew	0	5	1	2	0	0
	Patient ended protocol treatment	0	3	19	30	18	17
	Patient died	0	0	0	1	0	3
Difference (p-value[↑])		1% (0.45)	1% (0.59)	3% (0.46)	3% (0.62)	10% (0.10)	19% (0.002)

Supplemental Table S7b
Symptom and QOL Assessment Compliance

Measure	Treatment Arm	Evaluation Status	Baseline	Week 6	Week 10	Week 22	Week 34	Week 46
EORTC QLQ-C30/BN20	Placebo	**Form expected**	**248**	**236**	**192**	**130**	**88**	**68**
		Completed (%)	236(95%)	201(85%)	165(86%)	99(76%)	72(82%)	59(87%)
		Form expected, but not completed	7	14	16	13	5	4
		Patient refused due to illness	1	4	5	3	1	0
		Patient unable to be contacted	0	0	0	1	0	0
		Institutional error	3	3	4	1	1	1
		Tool not available in patients language	0	0	0	0	0	0
		Patient refused	1	4	4	5	2	3
		Other reason	0	1	3	2	1	0
		Out of timeframe	1	0	0	0	0	0
		Unknown	1	2	0	1	0	0
		Form expected, but not received	5	21	11	18	11	5
		Form not expected	**0**	**12**	**44**	**62**	**42**	**20**
		Patient progressed	0	3	25	41	29	13
		Patient withdrew	0	3	0	1	1	1
		Patient ended protocol treatment	0	6	19	19	12	6
		Patient died	0	0	0	1	0	0
	Bevacizumab	**Form expected**	**260**	**251**	**230**	**191**	**143**	**98**
		Completed (%)	249(96%)	220(88%)	192(83%)	157(82%)	107(75%)	76(78%)
		Form expected, but not completed	8	14	27	13	15	14
		Patient refused due to illness	0	5	7	1	6	3
		Patient unable to be contacted	0	0	0	0	0	0
		Institutional error	2	6	10	6	2	3
		Tool not available in patients	0	0	0	0	0	0

Supplemental Table S7b
Symptom and QOL Assessment Compliance

Measure	Treatment Arm	Evaluation Status	Baseline	Week 6	Week 10	Week 22	Week 34	Week 46
		language						
		Patient refused	2	2	5	2	5	3
		Other reason	1	1	3	1	1	4
		Out of timeframe	3	0	0	0	0	0
		Unknown	0	0	2	3	1	1
		Form expected, but not received	3	17	11	21	21	8
		Form not expected	**0**	**9**	**21**	**39**	**48**	**45**
		Patient progressed	0	1	1	6	30	25
		Patient withdrew	0	5	1	2	0	0
		Patient ended protocol treatment	0	3	19	29	18	17
		Patient died	0	0	0	2	0	3
	Difference (p-value[†])		<1% (0.74)	3% (0.43)	3% (0.48)	6% (0.19)	7% (0.20)	9% (0.12)
Measure	**Treatment Arm**	**Evaluation Status**	**Baseline**	**Week 6**	**Week 10**	**Week 22**	**Week 34**	**Week 46**
MDASI-BT	Placebo	**Form expected**	**248**	**236**	**192**	**130**	**88**	**68**
		Completed (%)	235(95%)	196(83%)	165(86%)	99(76%)	71(81%)	59(87%)
		Form expected, but not completed	10	17	15	14	7	4
		Patient refused due to illness	1	3	4	3	1	0
		Patient unable to be contacted	0	0	1	1	0	0
		Institutional error	5	7	2	2	2	1
		Tool not available in patients language	0	0	0	0	0	0
		Patient refused	1	4	6	5	2	3
		Other reason	1	2	2	2	2	0
		Out of timeframe	1	0	0	0	0	0

Supplemental Table S7b
Symptom and QOL Assessment Compliance

Measure	Treatment Arm	Evaluation Status	Baseline	Week 6	Week 10	Week 22	Week 34	Week 46
		Unknown	1	1	0	1	0	0
		Form expected, but not received	3	23	12	17	10	5
		Form not expected	**0**	**12**	**44**	**62**	**42**	**20**
		Patient progressed	0	3	25	41	29	13
		Patient withdrew	0	3	0	1	1	1
		Patient ended protocol treatment	0	6	19	19	12	6
		Patient died	0	0	0	1	0	0
	Bevacizumab	**Form expected**	**260**	**251**	**230**	**191**	**143**	**98**
		Completed (%)	244(94%)	214(85%)	191(83%)	154(81%)	107(75%)	74(76%)
		Form expected, but not completed	11	18	25	16	17	16
		Patient refused due to illness	0	4	5	2	7	5
		Patient unable to be contacted	0	0	0	0	0	0
		Institutional error	5	8	12	7	2	4
		Tool not available in patients language	0	1	0	0	0	0
		Patient refused	1	2	5	3	6	3
		Other reason	3	3	3	2	1	3
		Out of timeframe	2	0	0	0	0	0
		Unknown	0	0	0	2	1	1
		Form expected, but not received	4	18	13	20	18	7
		Form not expected	**0**	**9**	**21**	**39**	**48**	**45**
		Patient progressed	0	1	1	6	30	25
		Patient withdrew	0	5	1	2	0	0
		Patient ended protocol treatment	0	3	19	30	18	17
		Patient died	0	0	0	1	0	3

Supplemental Table S7b
Symptom and QOL Assessment Compliance

Measure	Treatment Arm	Evaluation Status	Baseline	Week 6	Week 10	Week 22	Week 34	Week 46
	Difference (p-value[↑])		1% (0.79)	2% (0.44)	3% (0.47)	5% (0.30)	6% (0.34)	11% (0.08)

Supplemental Table S8
Differences in Mean Score[a] for Measures that were Statistically Significantly Different[b] Between Arms

Patient Assessment	Outcome Measure	Time Points[#] 34 week	46 week
MDASI-BT[c]	Symptom Burden	0.206	0.326
	Symptom Inference	0.743	1.037
	Activity-related Interference	0.709	0.983
	Mood-related Interference	0.761	1.069
	Affective Factor	0.324	0.473
	Cognitive Factor	0.278	0.452
	Treatment Factor	0.45	0.616
	Generalized/Disease Factor	0.218	0.341
EORTC QLQ C30/BN20	Cognitive Functioning [d]	-4.778	-7.146
	Motor Dysfunction[e]	1.664	3.342
	Communication Deficit[e]	1.553	3.502
Neurocognitive Function[f]	TMT Part A	-0.666	-1.0223
	COWA	-0.334	-0.450
	Clinical Trial Battery Composite[g]	-0.405	-0.570

[a]Scores calculated as bevacizumab mean - placebo mean; [b]Based on longitudinal analysis; [c]Higher (positive) scores indicate greater symptom severity in the bevacizumab arm; [d]Lower (negative) scores indicate worse QOL in the bevacizumab arm; [e]Higher (positive) scores indicate worse QOL in the bevacizumab arm; [f]Standardized scores (z-scores), lower (negative) scores indicate greater cognitive dysfunction in bevacizumab arm;; [g]Clinical Trial Battery Composite = the average standardized z-score
[#]Data collection times were at baseline, 6, 10, 22, 34, and 46 weeks; 34 and 46 weeks were chosen to correspond with PFS estimates for each treatment arm.

Supplemental Figure S1
Protocol Schema